Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-126 and 129-131 were pending in this application and were rejected on various grounds. Claims 119-123 have been amended to remove references to the "gene amplification assay" and instead, now recite the functional recitation: "wherein said polypeptide inhibits the uptake of glucose or FFA (free fatty acids) by adipocyte cells." The previous rejections are discussed in view of the present claim amendments.

Continuity

Applicants have amended the pending claims to remove references to the "gene amplification assay." Applicants now rely on assay 94: Detection of polypeptides that affect glucose or FFA uptake by primary rat adipocytes (or 'the glucose/FFA uptake assay,' see Example 158, page 530 of the specification) for patentable utility of PRO1182 and its antibodies. This assay was first disclosed in International Application PCT/US00/08439, filed March 30, 2000, priority to which has been claimed in this application. As discussed below, the glucose/FFA uptake assay of the instant application, was a "well-established assay" that was well-known around the effective filing date of March 30, 2000. Hence, Applicants believe that they are entitled to at least an effective filing date of **March 30, 2000** for this application.

Claim Rejections – 35 USC § 101 and 112, first paragraph

Claims 119-131 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention lacks a credible, specific and substantial asserted utility or a well established utility."

Claims 119-131 are further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention".

Applicants now rely on assay 94: 'the glucose/FFA uptake assay,' instead of the "gene amplification assay" for patentable utility of PRO1182. The adipocyte glucose/FFA uptake assay was designed to determine whether a polypeptide is capable of modulating, either positively or negatively, the uptake of glucose or free fatty acids by adipocyte cells. The assay identifies

polypeptides that are useful for treating disorders wherein stimulation or inhibition of glucose uptake by adipocytes is therapeutically effective. Examples of such disorders include, but are not limited to, obesity, diabetes, and hyper- or hypo-insulinemia.

The adipocyte glucose/FFA assay of the instant application is performed as follows: primary rat adipocyte cells are plated on a 96 well plate and incubated overnight with media supplemented with PRO1182 polypeptide. After the initial overnight incubation, samples of the media are taken at hour 4 and hour 16 and residual glycerol, glucose and FFA are measured. After the hour 16 sample is taken, insulin is added to the media and the adipocytes are allowed to incubate for an additional 4 hours. After this final 4 hour incubation, another sample is taken and residual glycerol, glucose and FFA is measured again. As a control, identical incubations and samplings are performed on cells that have been incubated overnight in media initially supplemented with insulin rather than PRO1182 polypeptide. Results are scored as positive in the assay if the uptake is greater than 1.5 times (stimulatory) or less than 0.5 time (inhibitory) the uptake of the insulin control. As PRO1182 resulted in less than 0.5 the uptake of the insulin control, PRO1182 tested positive as an inhibitor of glucose/FFA uptake in adipocyte cells.

The glucose/FFA uptake assay, as described in Example 158 of the instant application, was a "well-established assay" around the effective filing date of March 30, 2000. Applicants show, by discussing prior publications that were available in the art around the effective filing date of March 30, 2000, that there was an art recognized nexus between proteins that tested positive in the adipocyte glucose/FFA assay and certain disease states. For example, it was well known in the art around March 30, 2000 that, increased glucose uptake by adipocyte cells was the hallmark of a number of therapeutically effective agents, such as troglitazone and poiglitazone. (Tafuri, *Endocrinology*, 137(11): 4706-4712 (1996); Sandouk, *et al.*, *Endocrinology*, 133(1):352-359 (1993) - copy enclosed with IDS). Both troglitazone and poiglitazone are members of the thiazolidinedione class of compounds and have been used to effectively treat noninusulin-dependent diabetes mellitus (NIDDM), the most common form of diabetes. Both compounds were shown to function, at least in part, by increasing the number of cellular glucose transporters in order to facilitate increased glucose uptake.

Further, vanadium salts were considered to be a potential treatment for diabetes, and several clinical trials had already been performed as of the effective filing date of Msrch 30, 2000

(see page 26617, right column, Goldwaser *et al.*, *J. Biol Chem.*, 274(37):26617-26624 (1999) - copy enclosed with IDS). Using the rat adipocyte culture system, similar to the system disclosed in the instant application, Goldwaser *et al.*, showed that vanadium ligand l-Glu (γ)HXM potentiates the capacity of free vanadium ions to activate glucose uptake and glucose metabolism in rat adipocytes *in vitro* by 4-5 folds and to lower blood glucose levels in hyperglycemic rats *in vivo* by 5-7 folds. Similar assays were commonly used to identify potential anti-diabetic agents and to examine the regulatory mechanisms of important molecules involved in fat cell metabolism.

Further, Mueller *et al.*, who were interested in determining the influence of glucose uptake on leptin secretion, employed essentially the same assay to measure changes in glucose uptake after insulin exposure. (Mueller *et al., Endocrinology*, 139(2): 551-558 (1998) - copy enclosed with IDS). Figure 1A showed the glucose concentrations in medium from 0-96 hours from isolated rat adipocytes in primary culture with various insulin concentrations. As indicated by the decrease in glucose in the medium in the Figure, Mueller *et al.* suggested that insulin produced a concentration-dependent increase in glucose uptake by the cultured adipocytes. Based on these experimental results, the authors stated that insulin increased leptin secretion over 96 hours, and that the increase in leptin was more closely related to the amount of glucose taken up by the adipocytes than to the insulin concentration, suggesting a role for glucose transport and/or metabolism in regulating leptin secretion. (See Abstract).

Using the same assay system, Mueller *et al.* further studied the effect of two well-known anti-diabetic agents, metformin and vanadium, on leptin secretion. These agents were known to enhance glucose uptake. (Muller *et al.*, *Obesity Research,* 8(7): 530-539 (2000) - copy enclosed with IDS). Mueller's experimental data indicated that both metformin and vanadium increased glucose uptake and inhibited leptin secretion from cultured adipocytes.

The studies discussed above clearly establish that the glucose/FFA uptake assay, as described in the instant application, is a well-established assay useful for identifying therapeutic agents for treating metabolic diseases such as obesity, diabetes, hyper- or hypo-insulinemia. Thus, Applicants respectfully submit that at the effective filing date of the present application, one skilled in the art would have reasonably accepted that molecules activating glucose uptake,

like PRO1182, would find real-life utilities in the treatment of metabolic diseases such as diabetes, obesity and related diseases.

In view of the above, Applicants respectfully submit that the specification discloses at least one credible, substantial and specific asserted utility for the polypeptide PRO1182. Accordingly, the Examiner is requested to reconsider and withdraw the present rejection under 35 U.S.C. §101 and §112, first paragraph.

Claim Rejections – 35 USC § 112, first paragraph- Written Description

Claims 119-131 are also rejected under 35 U.S.C. 112, first paragraph because, according to the Examiner, the subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing." Further, the Examiner contends that "the specification teaches a polypeptide (SEQ ID NO: 357) but does not teach functional or structural characteristics of all claimed polypeptides. The description of one PRO polypeptide (SEQ ID NO: 357) is not adequate written description of an entire genus of functionally equivalent polypeptides." Applicants respectfully traverse this rejection.

Arguments

Whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

Applicants have amended the claims to recite the functional recitation: "wherein said polypeptide inhibits the uptake of glucose or FFA (free fatty acids) by adipocyte cells" and rely on a well-established assay well-known to the skilled artisan at the effective filing date of this application. The claims encompass variant polypeptides of SEQ ID NO: 357 provided they "inhibits the uptake of glucose or FFA (free fatty acids) by adipocyte cells". Therefore, the polypeptides are defined both by functional as well as structural features. Since this assay was "well-established," one skilled in the art would know that the Applicants had possession of the

80-99% variants of SEQ ID NO: 357 that are positive in 'the glucose/FFA uptake assay.' Hence, Applicants request that this rejection be withdrawn.

Claim Rejections – 35 USC § 112, first paragraph- Deposit rules

Claims 119-124 and 129-131 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner contends that the ATCC deposit of the current invention needs the current address of the ATCC and a declaration or statement stating that all restrictions imposed by the depositor on the public be irrevocably removed.

Applicants submit that ATCC deposit No. 203088 was made under the Budapest Treaty, as indicated on page 566 and the address of the ATCC is correct as indicated on page 563, line 10 of the instant specification. Applicants have also added the requisite assurances in instant amendments to the specification that irrevocably remove all restrictions imposed by the depositor on the availability of deposited material to the public upon the granting of the pertinent U.S. patent. Accordingly, this rejection should be withdrawn.

Claim Rejections – 35 USC § 112, second paragraph

Claims 119-131 were rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. The Examiner contends that the claims are rendered indefinite because of "the phrase extracellular domain."

Without acquiescing to the propriety of this rejection and solely in the interest of expedited prosecution in this case, Applicants have canceled references to "extracellular domain" in the claims; that is part (c) and (d) of the claims have been deleted for clarity. Accordingly, Applicants submit that the claims are definite and respectfully request that this rejection be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C33).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: March 10, 2005

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